An approach to Process Development of pMDI's using Cold Fill and Pressure Fill Technology

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Summary

This paper discusses the manufacturing and process development approach taken from an early development stage through scale up and tech transfer to commercial manufacture. It gives background to both cold fill and pressure fill technology. Both methods are effective and have their specific advantages. It also sites comparisons and points to consider when assessing and selecting cold fill or pressure fill for the manufacture of pMDI's.

Projects, ideally are quick and inexpensive to develop, meet customer preferences without impact on the expectation of a single cycle review, are easy to routinely manufacture and batch release and tick all of the boxes that allow a product to be well marketed and available to patients at a competitive price to the health care provider.

At 3M, we continue to exercise our prior knowledge and experience, existing and new customer needs and embrace modern business models that advance the way in which we approach our development projects.

In order to realise these aims, it is important that the product development scientist and process development scientist work synergistically to develop a thorough understanding of what is required to 'realize' a successful commercial product. Holistic technical and indeed business decisions throughout the development cycle facilitate a smooth transition through product and process development, scale up, commercial manufacture and launch.

Introduction

Recent guideline changes and the introduction of QbD initiatives[1] further emphasise the requirement to understand the relationship between input raw materials, formulation, process design and product performance, that result in a robust yet flexible commercial validated manufacturing process[2,3]. This approach brings advantages such as a greater understanding of design space and process controls enabling efficient technology transfer of new products and processes into the commercial environment supplementing, lean manufacturing, continuous improvement programmes and sustainability initiatives.

An overview of the development cycle

Feasibility stage

Early phase batches are typically manufactured at lab scale, filling anything from single containers to small scale batches of 100's of units. It is at this stage of the project that product and process scientists should give consideration to all factors that may influence product and process viability, providing valuable insights to enable future risk management.

Pilot Scale

To bridge the transition between lab and full scale, pilot scale batches, of 1000's of units, are manufactured on equipment more representative of the commercial manufacturing process. At this scale, multiple batches can be manufactured and equipment cleaning experiments can be performed without the need to use the commercial manufacturing facility resulting in reduced project costs and future risks. This is particularly effective where new and novel materials are both expensive and potentially in short supply.

Commercial Scale Manufacturing Options

It is the expectation that the product and process development scientist will manage and mitigate all significant risks through laboratory and pilot scale development to allow seamless introduction of new and /or novel processes into the commercial facility. This allows for the completion of equipment designs and fabrication and qualification of manufacturing equipment specific to product needs.

pMDI Manufacturing Process Overview

There are two major approaches to pMDI manufacture, cold filling and pressure filling[4]. Both processes are an effective means of commercialising products and have their advantages dependant on the nature of the product or formulation being manufactured. See table 1 for points to consider.

Two major types of formulation exist namely suspension and solution, and each will demand different factors to be considered to enable successful commercialisation. Both approaches demand careful development and understanding to establish critical process parameters which need to be optimised, justified, measured and controlled throughout the manufacturing process.

Figure 1 provides an overview of typical factors that should be considered through the development cycle for both product and process from the laboratory feasibility stage to the full scale commercial facility.

The general principles of manufacture for pMDIs involve 5 main stages:-

- Propellant batching
- Concentrate preparation
- Canister Filling
- Post Filling Activity
- Equipment Cleaning

Propellant Batching

Since the propellants used in pMDI's are gaseous at normal temperature and pressures they must be liquefied to enable manufacturing equipment to process them efficiently. Liquification can be achieved either by lowering the temperature, (cold filling) or by applying pressure (pressure filling).

Cold Filling: Volatile propellants are liquefied by chilling below their boiling point in a refrigerated vessel, where typical temperature ranges from -50°C to -60°C.

Pressure Filling: Pressure is used to condense the propellant. The propellant is held in a pressurised vessel in liquid form typically at 100 psi.

Concentrate Preparation

This involves the creation of a concentrate by mixing the active pharmaceutical ingredient (API) with a solvent or carrier that is liquid at room temperature. This is transferred to the batching vessel on completion. Consideration should be given to the stability of the input raw materials (physical and chemical), so that appropriate choices can be made regarding routes and orders of addition and whether to formulate the concentrate as either a suspension or solution. Additionally in the case of cold filling it may be appropriate to manufacture the concentrate as a chilled liquefied propellant mixture.

Typical factors that are considered at this stage include; material handling and isolation, rates, orders and methods of addition, temperature ranges, pressure ranges, mixer speeds, pump speeds, etc.(see figure 1).

Canister Filling

Cold Filling: The concentrate is pre-mixed with the volatile propellant at low temperature within the batching vessel, and formulation is then dispensed directly in a single filling step into the empty pMDI canister and the metering valve is then crimped into place. Cold filling does not require any formulation to be driven through the valve.

Pressure Filling: There are two main variants of pressure filling, the two-stage method and the single stage method, though the industry is currently almost entirely single stage.

In the single stage pressure filling method, the concentrate is pre-mixed with the volatile propellant under pressure within the batching vessel, and formulation is then injected through a pre-crimped metering valve and canister.

In the two-stage pressure filling method, a concentrate of active drug and excipients are filled into the empty canister. A valve is then placed and crimped to the part filled canister and the volatile propellant injected through the metering valve.

Both two-stage and single-stage pressure filling rely on a step in which material is driven backwards through the valve at high pressure, as opposed to the normal patient-use operation in which the valve opens to allow formulation out of the canister.

Post Filling Activity

Post filling of product manufactured by either route involves typical in process controls of fill weight, crimp dimension checks as well as heat stress challenge and function testing before through batch units are sampled for product release testing according to the specification.

Equipment Cleaning

Cleaning development is an integral part of the process development phase[5], with the expectation that cleaning data is generated at an early part of the project. 'If you can't clean it, you can't make it'. Dedicated equipment is verified as visibly clean including any hot spots. Non dedicated, shared equipment is verified as clean to an Acceptable Residual Limit which considers the toxicity of the API and excipients and cleaning materials used as well as equipment design and the nature of the follow on products. Cleaning methods are developed, optimised, confirmed and validated.

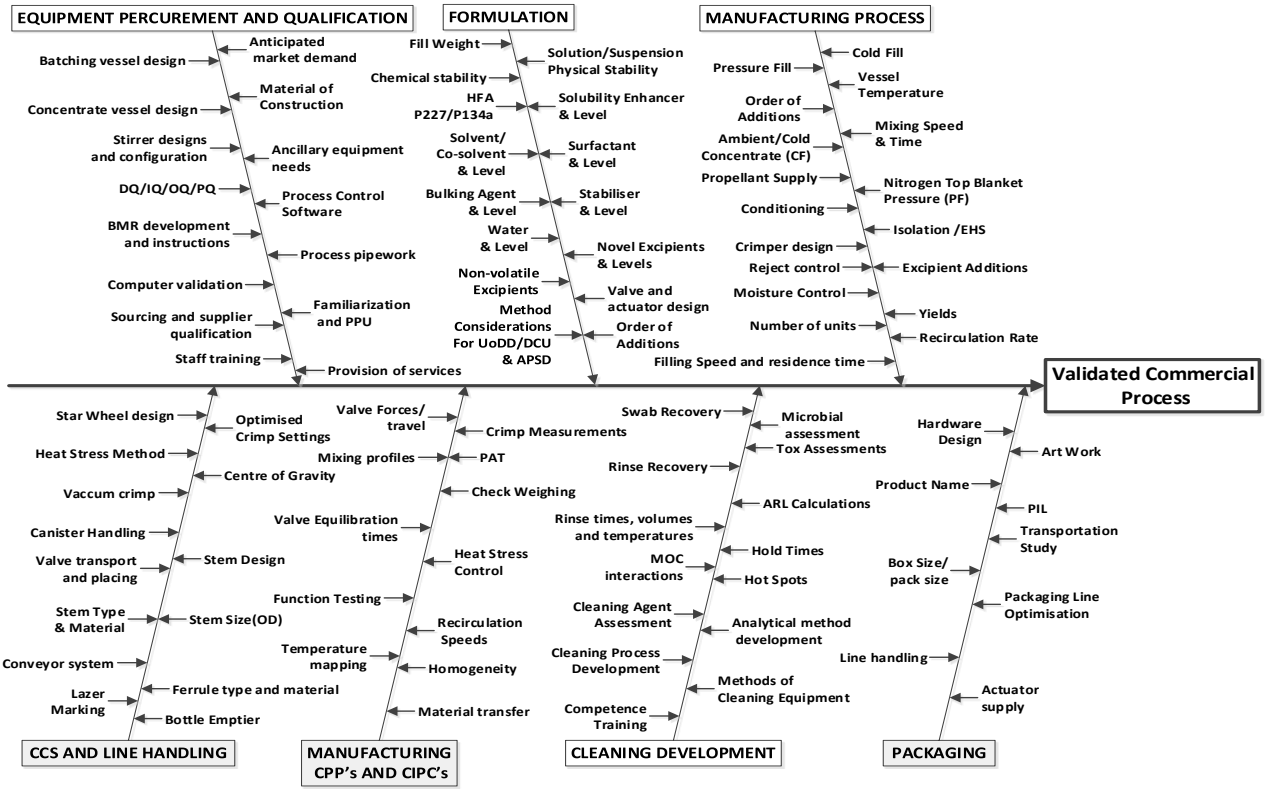

Figure 1 Overview of typical factors that should be considered through the development cycle

Point to consider	Cold Fill	Pressure Fill
Filling Speed per unit	Faster per unit as filled directly into open canister	Slower per unit as filled through valve but multi head off the shelf equipment available
Formulation type	Capable of filling solutions or complex suspensions	Process lends itself to filling solutions more easily
Formulation	Very low, to high powder loading Suspensions APIs in which the particle size must be closely controlled during formulation Solution formulations that can tolerate low temperature [6]	Solutions with API that easily dissolves in an ethanol/propellant formulation Certain suspensions with very low to moderate powder loading and a very small amount of drug relative to the formulation
Valve selection	Any valve	Only pressure fillable valves can be used
Process Equipment Considerations	Requirement for refrigeration and MOC that will tolerate low temperatures	Requirement for high pressure rating and MOC that will tolerate high pressure and provide effective sealing
Fill weight accuracy	Important for accuracy of number of shots to patient	Same importance in single stage Twin stage is critical as final drug content is also impacted
Requirement to purge units	No requirement	Unit must be purged or vacuum crimped

Table 1. Comparison of Cold and Pressure fill

Conclusion

Modern process development demands a dynamic approach to enable efficient and effective outcomes which will produce reliable high quality product with low risk, satisfying high regulatory standards and the ever changing demands of the commercial world.

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